REMARKS

A. Status of the Claims

Claims 1-31 are pending, of which claims 11-23 and 26-30 are withdrawn an claim 31 is new. Claims 1, 6, 8, 9 and 10 have been amended. No new matter has been added. Support for the amendment to claim 1 and new claim 31 can be found in the specification at least at the top of page 4, page 21, bottom of page 43, etc.

B. Claim Objections

Claim 8 has been amended as requested.

Applicants respectfully traverse the objection as to claims 24 and 25, noting that the non-elected claims are still pending.

C. Specification

The specification has been appropriately amended.

D. Section 112, Second Paragraph Rejections

The claims have been amended in a manner that is believed to address the Examiner's concerns. Support for stringent hybridization conditions can be found at the bottom of page 23, referencing the Sambrook *et al.* laboratory manual.

E. Section 112, First Paragraph Rejection

The Action next rejects all of the claims, taking the position that the subject matter of these claims is not fully enabled:

(i) for 7-transmembrane receptors such as proto-oncogenes and

(ii) for such G-protein coupled receptors labelled in the <u>first</u> cellular loop and the carboxy-terminus.

In particular, it is alleged that the skilled person "cannot use all 7-transmembrane receptor[s] to label the third or first intracellular loop because ... the labelling with large insert with fluorescent protein into the third or first intracellular loop will sterically disrupt the interaction with G-protein or other functional activator in the intracellular region" (emphasis added). It is further alleged in this context that one skilled in art cannot predict the outcome of changes to protein structure using large fluorescent protein insertion into important structural domains and that no working example is provided to determine whether a change in the first intracellular loop would provide proper function.

First, it is respectfully noted that to maintain a *prima facie* enablement rejection the Examiner is required under MPEP Section 2164.04, to provide specific reasons to doubt the objective truth of the statements contained in the specification, and to back up such assertions with reasons and, preferably, evidence:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "***it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.*** Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370.

MPEP Section 2164.04 (emphasis supplied). In the present case, the Action merely makes some assertions about steric hindrance and folding hindrance, without providing any documented support for these statements, or that steric hindrance is an issue in the context of the present invention. The Action goes on to mention that receptors have specific folding function, referencing a Methods in Enzymology article. However, the Action provides no evidence nor points us to any passage from the article to support a conclusion that any such folding would in any way interfere with the practice of the present invention. Thus, no *prima facie* enablement rejection has been properly set forth.

Moreover, as apparently acknowledged by the Examiner, the present application convincingly demonstrates that prominent members of 7-transmembrane receptors, "namely the α_{2A}–adrenergic (neurotransmitter) receptor, the (adenosine) A2A-receptor and the parathyroid hormone (PTH hormone) receptors" (see, e.g., page 7, bottom, of the specification), can indeed successfully be employed in accordance with the present invention (e.g. in the context of a reliable, fast an easy measurement of the activation of 7-transmembrane proteins"; see page 6 and 7 bridging paragraph, of the specification). We submit that this makes it clear that the present application provides evidence that 7-transmembrane receptors can generally be employed successfully in accordance with the teaching of the present application. Further evidence of enablement can be found in the fact that we have shown that a FRET-fluorophore does not negatively affect the receptor function, even if it is inserted into the <u>first</u> intracellular loop (see, e.g., Fig. J as enclosed). Thus, there is no reason (and no reason elucidated) that the introduction of FRET-fluorophores into <u>other</u> 7-transmembrane receptors will negatively effect their function.

In order to support the above line of argument that the examples provided in the present application can be generalized to basically all 7-transmembrane receptors, we herewith provide

examples of further 7-transmembrane receptors which have successfully been used in accordance with the present invention. These further examples of 7-transmenbrane receptors are:

(a) the human M1-muscarinic receptor (Figure A and B),

(b) the human M3-muscarinic receptor (Figure C and D),

(c) the human M5-muscarinic receptor (Figure E) and

(d) the human H1-histamine receptor (Figure G and H).

Each of the foregoing were labelled at the third intracellular loop and the C-terminus with the combination of FlAsH and CFP. Figures A, C, E and G display the ratio between the CFP and FlAsH fluorescence, whereas Figures B, D and H display the CFP and FlAsH traces separately. Figure F displays the concentration-effect relationship for the M1, 3 and 5 muscarinic receptors which further underscores the utility of the recombinant 7-transmenbrane constructs of the present invention. All of the above exemplified further 7-transmembrane receptors have already been mentioned in the application as originally filed (see, e.g., page 40, middle) and belong to the group of G-protein-coupled receptors.

We submit that the foregoing provides strong evidence that the teachings of the present invention are broadly applicable to 7-transmembrane receptors in general.

As further supporting data that also the first intracellular loop can be labelled in order to create functional 7-transmembrane receptor constructs in accordance with the present invention, Figure J is provided. Figure J shows the activation of the mouse α_{2A}–adrenergic receptor via its effector ("NE"). The receptor has been labelled in the first intracellular loop and the C-terminus. The data show that also an introduction of a fluorofore into the first intracellular loop leads to the formation of a functional recombinant 7-transmembrane receptor which can be used in accordance with the present invention.

For the foregoing reasons, the Examiner is respectfully requested to reconsider and withdraw the enablement rejections.

F. Anticipation Rejections

In response to the anticipation rejections over Altenbach and Kobilka, it is respectfully pointed out that neither of these references describe the use of two labels that are both detectable by resonance energy transfer detection methods. Altenbach indeed describes a 7-transmembrane receptor comprising two nitroxide labels. However, such labels are not detectable by RET. Similarly, Kobilka describes a 7-transmembrane receptor construct comprising a fluorescent label and a poly-his-tag, the latter of which is used for purification but not for a detection via RET-technology.

The present invention focuses on intramolecular RET-technology for detecting conformation changes within the 7-transmembrane receptor molecule. Accordingly, the two detectable labels as comprised in the claimed recombinant 7-transmembrane receptor are RET-labels that allow resonance energy transfer to occur between them.

For the foregoing reasons, the Examiner is respectfully requested to reconsider and withdraw the anticipation rejections.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3055 is respectfully requested.

Respectfully submitted,

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